II. REMARKS

Preliminary Remarks

Claims 1 and 4 are amended and claims 10-15 are canceled. Upon entry of the amendment, claims 1, 4-9, and 16-25 will be pending.

Step (a) of claim 1 is amended to specify programming the start of a treatment cycle comprising COS by inducing the start of menses by administering LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix, wherein the LHRH antagonist is administered at a dosage range between 0.5 mg to 10 mg during the luteal phase of the menstrual cycle preceding the treatment cycle.

Claim 4 is similarly amended by deleting reference to administering an agent for programming the start of a treatment cycle comprising COS selected from a progestogen only preparation, a combined oral contraceptive preparation, or a combination comprising a progestogen only preparation or a combined oral contraceptive preparation.

Claims 10-15, which identify the agent of step (a) of claim 1 as a progestogen preparation or a combined oral contraceptive preparation, are canceled.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Patentability Remarks

35 U.S.C. §112, first paragraph, written description

Claims 1 and 4-25 are rejected under 35 U.S.C. §112, first paragraph, for lack of written description, because the application is not considered to provide descriptive support for the claimed method wherein a progestogen only preparation and/or a combined oral contraceptive preparation is administered "during the luteal phase of the menstrual cycle prior to the preceding menstrual cycle." Please note that rejected claims 10-15 are canceled.

As noted above, the section of step (a) of claim 1 which specifies administering a progestogen only preparation and/or a combined oral contraceptive preparation "during the luteal phase of the menstrual cycle prior to the preceding menstrual cycle" is deleted. Withdrawal of the rejection of pending claims 1, 4-9, and 16-25 under 35 U.S.C. §112, first paragraph, for lack of written description, is therefore respectfully requested.

35 U.S.C. §112, second paragraph

Claims 1 and 4-25 are rejected under 35 U.S.C. §112, second paragraph, because the precise meaning of the expression "prior to the preceding menstrual cycle" in step (a) of claim 1 is considered to be unclear. Again, please note that rejected claims 10-15 are canceled.

As noted above, the section of step (a) of claim 1 which specifies administering a progestogen only preparation and/or a combined oral contraceptive preparation "during the luteal phase of the menstrual cycle prior to the preceding menstrual cycle" is deleted. Withdrawal of the rejection of pending claims 1, 4-9, and 16-25 under 35 U.S.C. §112, second paragraph, for indefiniteness, is therefore respectfully requested.

35 U.S.C. §103(a)

A. Claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-25 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of Felberbaum et al. (1997) or Albano et al. (1996) or Engel et al. (1997) or Olivennes et al. (1994), considered in combination with Ziegler et al. (1998), and further in combination with Garfield et al. (U.S. Patent No. 5,470,847) or Hall et al. (1991). As claims 1 and 4 are amended and claims 10-15 are canceled, the statement of the rejection is addressed as it applies to pending claims 1, 4, 5, 7, 16, 18, and 21-25.

The four alternative primary references (Felberbaum et al., Albano et al., Engel et al., and Olivennes et al.) describe protocols based on known and commonly applied procedures for carrying out ovarian stimulation (OS) and assisted reproductive techniques (ART) in normal physiologic menstrual cycles. Felberbaum et al., Albano et al., Engel et al., and Olivennes et al. each describes a normal controlled ovarian stimulation (COS) procedure in which HMG is administered starting on day 2 of the treatment cycle for ovarian stimulation, and an LHRH antagonist is administered starting on day 4 or 5 of the cycle to prevent premature ovulation,

HCG is administered when a sufficient number of follicles of sufficient diameter was observed, and oocytes are recovered and used in the application of ART.

The cited primary references do not describe or suggest a method for therapeutic management of infertility and increasing the quality of fertilized oocytes and embryos by programming COS and ART, which method comprises programming the start of a treatment cycle comprising COS by inducing the start of menses by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the luteal phase of the menstrual cycle preceding the treatment cycle, as specified in claim 1.

The examiner cites Ziegler et al. as teaching the desirability of timing the onset of controlled ovarian hyperstimulation (COH), and alleges that at the time the invention was made it would have been obvious for one of ordinary skill in the art to modify a method for COS and ART as described by Felberbaum et al., Albano et al., Engel et al., or Olivennes et al., "by providing advanced timing via administration of a composition to allow for improved scheduling of treatments," with "the expectation of improving the efficiency of treatment scheduling and thus fertilization success with the advanced timing method." *See* pages 10-11 of the official action.

The examiner describes Garfield et al. as teaching that a progesterone-only or a combined estrogen-progesterone preparation can be administered as an oral contraceptive that inhibits the synthesis of LHRH and prevents the LH surge required for ovulation (for example, *see* col. 2, lines 17-47). *See* page 11 of the official action. Please note that Garfield relates to subject matter that is deleted from the currently pending claims.

The examiner cites Hall et al. for its teaching that administering three daily doses of the LHRH antagonist Nal-Glu during the mid-luteal phase caused "dramatic" decreases in blood concentrations of estrogen and progestogen, and induced luteolysis and the onset of menstrual bleeding within 24-48 hours after the final day of LHRH antagonist administration in all subjects. *See* page 997, bottom of left column. The examiner observes that the LHRH antagonist was administered with a dosage of 150 μg/kg, and alleges that it would have been obvious to vary or optimize the amount of LHRH antagonist administered during the luteal phase as the determination of optimum or workable ranges is routine experimentation. The examiner

alleges that it would have been obvious to combine the methods of the primary references with that of Ziegler et al., to obtain a method of programming the timing of COS/ART in which an estrogen-only preparation is administered during the cycle preceding COS/ART that comprises administering an LHRH antagonist during the follicular phase, and then to further modify said method to administer an LHRH antagonist during the preceding cycle to induce the timed onset of menstrual bleeding prior to the start of COS/ART procedures, in view of the teachings of Hall et al. regarding LHRH antagonists. *See* page 13 of the official action. While Hall et al. does not disclose administering an LHRH antagonist specified in claim 1 (*i.e.*, cetrorelix, teverelix, ganirelix, antide, or abarelix), the examiner alleges that it would have been obvious to do so since these are disclosed in the primary references. *See* pages 11-13 of the official action.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re* Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. *In re* Merck & Co., Inc., 800

F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. *In re* Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Combining prior art references without evidence of a suggestion, teaching, or motivation "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." *See* Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1371-72; 56 U.S.P.Q.2d 1065 (C.A.Fed. - Cal., 2000).

The applicants respectfully submit that the examiner has not established a *prima facie* case of obviousness, because the cited references would not have provided one of ordinary skill in the art with a suggestion or motivation to modify a normal method for COS and ART such as a protocol described by Felberbaum et al., Albano et al., Engel et al., or Olivennes et al., by administering a LHRH antagonist selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, and abarelix during the luteal phase of the menstrual cycle preceding the treatment cycle, in order to program the start of a treatment cycle comprising COS by inducing the start of menses, in accord with the claimed invention. Furthermore, one of ordinary skill in the art at the time the invention was made would not reasonably have expected that a method for COS and ART that is modified by administering a LHRH antagonist during the luteal phase of the menstrual cycle preceding the treatment cycle in order to induce luteolysis and the start of menses as described by Hall et al. would operate successfully, due to deleterious or disruptive effects of gonadotropin deprivation caused by the LHRH antagonist on the physiological and biochemical processes required for oocyte development, as discussed below.

No suggestion or motivation to modify or combine the cited references

As discussed above, the four primary references, Felberbaum et al., Albano et al., Engel et al., and Olivennes et al., describe protocols for COS and ART comprising administering HMG starting on day 2 of the treatment cycle for ovarian stimulation, administering an LHRH antagonist during the follicular phase of the cycle to prevent premature ovulation, administering

HCG to induce ovulation, recovering oocytes and applying ART. None of the primary references describe or suggest performing the claimed method of COS and ART comprising programming the start of the treatment cycle by inducing the start of menses by administering a LHRH antagonist during the luteal phase of the menstrual cycle preceding the treatment cycle.

Ziegler et al. describe a method for "timing assisted reproductive techniques (intrauterine insemination and in-vitro fertilization) in the natural cycle" that comprises administering estradiol starting about 7 days before the onset of menses and continuing for about 5 days, until the first Tuesday following the onset of menses, defined as functional day (FD) 0; starting daily administration of HMG on FD3 (Friday) that is continued for about 11 days, on average, of HMG treatment; and then administering HCG to induce ovulation. The method of Ziegler et al. delays the intercycle elevation of FSH but does not affect the timing of the onset of menstrual bleeding, which is described as being regulated by progesterone (*see* page 562, right column). Ziegler et al. expressly describe their method as one that permits an advanced timing of the onset of controlled ovarian hyperstimulation (COH) treatments "when gonadotrophin-releasing hormone (GnRH) agonists are not used," and as having practical applications for timing ART "in the natural cycle." *See* page 561, left column. Thus, Ziegler et al. expressly teaches away from modifying a normal COS/ART procedure that include administering an LHRH antagonist during the follicular phase to suppress premature ovulation so as to obtain a method that comprises administering a LHRH antagonist during the preceding cycle to induce the timed onset of menstrual bleeding.

The examiner alleges that it would have been obvious to combine the methods of the primary references with that of Ziegler et al., in view of Hall et al. to obtain a method of programming the timing of COS/ART in which an LHRH antagonist is administered during the preceding cycle to induce the timed onset of menstrual bleeding prior to the start of COS/ART procedures, "with the expectation of providing control of menstrual phases to provide advanced timing" for ART (*see* page 13 of the official action). However, contrary to the examiner's allegation, one of ordinary skill in the art at the time the invention was made would not reasonably have expected that a method for COS and ART that is modified by administering a LHRH antagonist during the luteal phase of the menstrual cycle preceding the treatment cycle in order to induce the start of menses would operate successfully for carrying out controlled ovarian

stimulation (COS) and assisted reproductive techniques (ART). Scientific articles published at the time the invention was made would have led one of ordinary skill in the art to expect that administration of an amount of LHRH antagonist during the luteal phase sufficient to induce luteolysis and the start of menses could have deleterious effects on oocyte meiosis and the mitotic programs of cells undergoing folliculogenesis, blastomere formation and endometrium development, during the following cycle. LHRH antagonists were considered to have potentially deleterious effects mediated by mechanisms separate from their effects on gonadotropin levels. For example, LHRH antagonists were considered to be capable of compromising the mitotic program of cells undergoing folliculogenesis, blastomere formation and endometrium development by inhibiting the synthesis of growth factors and through direct interactions with the LHRH receptor (*e.g., see* the abstract of Hernandez, 2000, Human Reproduction 15(6):1211-1216). LHRH antagonists were also considered to be capable of interfering with mechanisms involved in germinal vesicle breakdown and the cell signaling pathway driving the oocyte into metaphase II (*e.g., see* De la Fuente et al, 1999, Human Reproduction, 14: 3060-3068). Hall et al. reported that the cycle following induction of luteolysis by an LHRH antagonist was lengthened by about 6 days, and stated that further study is needed to determine if this difference is the result of altered gonadotropin dynamics after administration of the antagonist and possible effects of these on the developing follicle" (*see* page 999, middle of left column). Accordingly, prior to the successful demonstration of the efficacy of the claimed invention by the present applicants, it was not known if the timing of successful COS/ART procedures could be effectively programmed by administering a dosage of an LHRH antagonist during the luteal phase of the preceding cycle that induces the start of menses. Rather than having a deleterious effect upon the developing oocyte and supportive tissues, the claimed method provides for successful programming of COS/ART procedures with the surprising advantage that follicular development is coordinated so that an increased number of high quality, mature follicles of similar size is produced for ART, as described in the Declaration of Dr. Riethmüller-Winzen that was submitted with the previous response.

In view of the foregoing, withdrawal of the rejection of claims 1, 4, 5, 7, 16, 18, and 21-25 under 35 U.S.C. §103(a) as having been obvious in view of Felberbaum et al. or Albano et al.

or Engel et al. or Olivennes et al., in combination with Ziegler et al. (1998), and further in combination with Garfield et al. or Hall et al., is respectfully requested.

B. Claims 6, 8, 9, 17, 19, and 20 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of (i) Felberbaum et al. (1997) or Albano et al. (1996) or Engel et al. (1997) or Olivennes et al. (1994), considered in combination with (ii) Ziegler et al. (1998), and further in combination with (iii) Garfield et al. or Hall et al. (1991), as applied to claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-25, and further in view of Deghengi (U.S. Patent No. 5,945,128) or Rabasseda (1999).

The teachings of Felberbaum et al., Albano et al., Engel et al., Olivennes et al., Ziegler et al., Garfield et al., and Hall et al., as applied by the examiner to claims 1, 4, 5, 7, 16, 18, and 21-25, are discussed above.

Deghengi is described by the examiner as teaching that cetrorelix, teverelix, ganirelix, and antide were known to be the LHRH antagonists.

Rabasseda is described by the examiner as teaching that LHRH antagonists such as cetrorelix, ganirelix, and ibarelix were known to be useful for treating female infertility.

As discussed above, one of ordinary skill in the art at the time the invention was made would not have been motivated to combine the methods of the primary references with that of Ziegler et al., in view of Garfield et al. or Hall et al., to obtain a method of programming the timing of COS/ART in which a LHRH antagonist, is administered during the preceding cycle to induce the timed onset of menstrual bleeding prior to the start of COS/ART procedures, and would reasonably have expected that such a method would be associated with deleterious effects that would prevent successful operation of the COS/ART procedures, as discussed above. The teachings of Deghengi and Rabasseda regarding the disclosed LHRH antagonists do not remedy the deficiencies of the cited references discussed above to establish a *prima facie* case of obviousness under 35 U.S.C. §103(a). Accordingly, withdrawal of the rejection of claims 6, 8, 9, 17, 19, and 20 under 35 U.S.C. §103(a) as having been obvious in view of Felberbaum et al. or Albano et al. or Engel et al. or Olivennes et al., in combination with Ziegler et al. taken with Garfield et al. or Hall et al., and further in view of Deghengi or Rabasseda, is respectfully requested.

C. Claims 12-15 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of (i) Felberbaum et al. (1997) or Albano et al. (1996) or Engel et al. (1997) or Olivennes et al. (1994), considered in combination with (ii) Ziegler et al. (1998), and further in combination with (iii) Garfield et al. or Hall et al. (1991), as applied to claims 1, 4, 5, 7, 10, 11, 16, 18, and 21-24, and further in view of Kent (U.S. Patent No. 4,016,259). As noted above, claims 12-15 are canceled and the statement of rejection is moot.

Judicially Created Doctrine of Obviousness Double Patenting

Claims 1 and 4-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and Kent, as applied above. As claims 10-15 are canceled, the statement of the rejection is addressed as it applies to pending claims 1, 4-9, and 16-25.

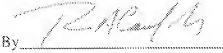
The applicants submit that at the time the invention was filed, one of ordinary skill in the art would not have been motivated to combine the method of claims 1-6 of U.S. Patent No. 6,319,192 with that of Ziegler et al., in view of Garfield et al., Hall et al., Deghengi, Rabasseda, and Kent, to obtain a method of programming the timing of COS/ART in which a LHRH antagonist is administered during the preceding cycle to induce the timed onset of menstrual bleeding prior to the start of COS/ART procedures, with a reasonable expectation of success. One of ordinary skill in the art at the time the invention was filed could not reasonably have predicted the effects of administering a LHRH antagonist during the preceding cycle to induce the timed onset of menstrual bleeding prior to the start of COS/ART procedures, and would reasonably have expected such a step to cause deleterious effects that would prevent successful operation of the COS/ART procedures, as discussed above. Accordingly, withdrawal of the rejection of claims 1, 4-9, and 16-25 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,319,192 of Engel et al., in view of Ziegler et al., Hall et al., Deghengi, Rabasseda, and Kent, as applied above, is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

Date: April 25, 2007 By 

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